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Dear Professor Ghosez:

Please find enclosed our revised manuscript number (TET-D-06-00384) which has been modified according to referee's suggestions:

- 1) In order to shorten the paper, part of the results have been removed, and only the reactivity of different dihalides is reported.
- 2) The title has been change to "Arene-promoted lithiation of 1,n-dihaloalkanes (n = 2-6): A comparative study".
- 3) The body text of part 2. Results and Discussions has been divided in two subchapters:
2.1. Lithiation of 1,n-dihaloalkanes 3 under Barbier reaction conditions (Method A)
2.2. Lithiation of 1,n-dihaloalkanes 3 under Grignard reaction conditions (Method B)
- 4) Compounds and intermediates have been renumbered in order to avoid confusion. All compounds have been referred to in Arabic characters.
- 5) Table 2 has been modified from 20 entries to 15 entries due to the elimination of 1,n-bis(phenylsulfanyl)derivatives.
- 6) Scheme 2, tables 3 and 4 along with the text related to this scheme and these tables in Results and Discussions have been removed.
- 7) In Experimental, former subchapters 4.2., 4.3., 4.6. and 4.7. have been removed.
- 8) Former references 3, 4, 18 and 20-25 have been removed.
- 9) Graphical Abstract has been modified.

Arene-promoted lithiation of 1,n-dihaloalkanes (n = 2-6): A comparative study

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Abstract- The reaction of 1,n-dichloroalkanes **3a** (n = 2-6) with an excess of lithium powder and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB; 2.5 mol %) in the presence of different carbonyl compounds [Bu^tCHO, PhCHO, Et₂CO, (CH₂)₄CO, (CH₂)₅CO, (CH₂)₇CO, (-)-menthone], in THF at -78 °C leads, after hydrolysis with water, to the expected 1,(n+2)-diols **4**, yields being < 25% for n = 2, 3 and in the range of 45-79% for n = 4-6. When the same protocol is applied to 1,n-bromochloroalkanes **3b** and 1,n-dibromoalkanes **3c** (n = 2-6), diols **4** are obtained in general with lower yields.

1. Introduction

From a synthetic point of view, the generation of dilithio compounds¹ of the type **1** (Chart 1) would be of great interest because their reaction with two molecules of an electrophile would allow the simultaneous introduction of two electrophilic fragments in the starting molecule through a single synthetic operation. The halogen-lithium exchange² is the most commonly used method to generate these intermediates, but this methodology can not be applied in this case because the initially formed halogen-lithium compound **2** (Chart 1) is extremely unstable and suffers spontaneous elimination of lithium halide, so preventing the second lithiation step.³ Thus, **2** with n = 1, the so-called lithium carbenoids, undergo α-elimination giving a carbene, which either decompose or can be trapped by an appropriate reagent.⁴ Probably, the most dramatic situation appears for **2** with n = 2, where the β-elimination affording an olefin occurs rapidly, even at very low temperatures (< -100 °C),⁵ making impossible to prepare this type of intermediates and, consequently, the corresponding 1,2-dilithio compounds. In the case of n = 3, it has been shown that the γ-elimination, that gives a cyclopropane derivative, works no so easily so, in some cases, the corresponding γ-functionalised organolithium compound can be trapped under mild reaction conditions.⁶ For intermediates **2** with n = 4-6 the elimination can be avoided partially under controlled reaction conditions,⁷ which in general consist in performing the lithiation using an arene as electron carrier⁸ at low temperature and in the presence of the corresponding electrophile (Barbier-type reaction conditions⁹). In the frame of our continuous interest on the lithiation of compounds of type **3**¹⁰ (Chart 1) we report here the 4,4'-di-*tert*-butylbiphenyl (DTBB)-catalysed lithiation of different 1,n-dihaloalkanes **3a-c**¹¹ and their use as 1,n-dianionic synthetic equivalents in the reaction with different carbonyl compounds as electrophiles.

Keywords: DTBB-catalysed lithiation; halogen-lithium exchange; electrophilic substitution; symmetric diols.

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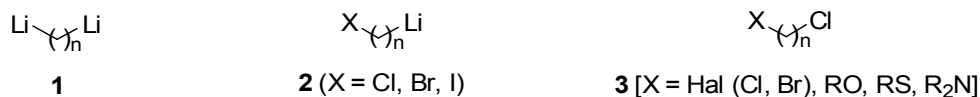
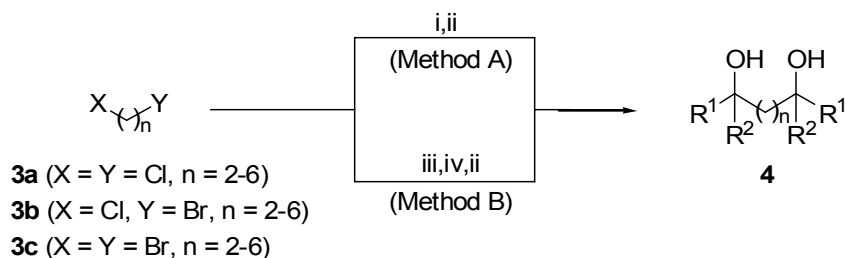


Chart 1.

2. Results and Discussion

2.1. Lithiation of 1,n-dihaloalkanes **3** under Barbier-type reaction conditions (Method A)

The reaction of commercially available 1,n-dichloroalkanes **3a** with an excess of lithium (1:10 molar ratio; theoretic 1:4 molar ratio) and a catalytic amount of DTBB (1:0.1 molar ratio, 2.5 mol %) in the presence of different carbonyl compounds (1:3 molar ratio) in THF at -78°C for *ca.* 3 h, followed by hydrolysis with water at temperatures ranging between -78°C and room temperature (Method A), led the diols **4** (Scheme 1 and Table 1).

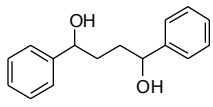
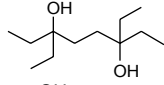
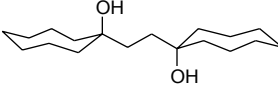
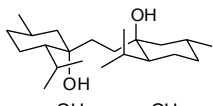
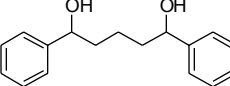
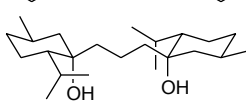
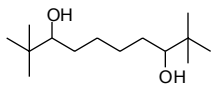
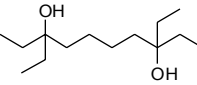
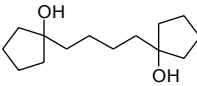
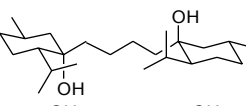
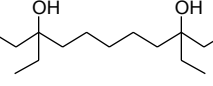
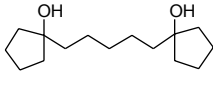
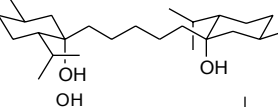
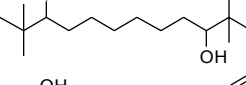
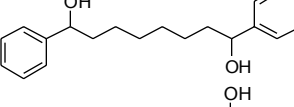
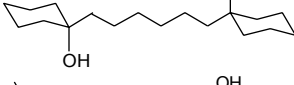
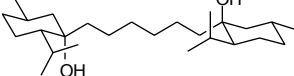


Scheme 1. Reagents and conditions: (i) Li, DTBB (2.5 mol %), $\text{R}^1\text{R}^2\text{CO}$, THF, -78°C ; (ii) H_2O , -78 to 20°C ; (iii) Li, DTBB (2.5 mol %), THF, -78°C ; (iv) $\text{R}^1\text{R}^2\text{CO}$, -78°C

As expected, yields are low for compounds **4** with $n = 2, 3$ due to the above commented elimination side reaction problems, which gave ethylene and cyclopropane, respectively (Table 1, entries 1-6). However, in the other cases (**4** with $n = 4-6$) this problem was extensively overcome, so the expected diols were the main products isolated (Table 1, entries 7-17). When aldehydes were used as prochiral electrophiles, the corresponding *ca.* 1:1 mixtures of diastereomers (NMR) were obtained (Table 1, entries 1, 5, 7, 14 and 15, and footnote c). In the case of (-)-menthone, the attack of the organolithium intermediate to the upper less hindered face of the chiral electrophile¹² was exclusively observed, so the corresponding enantiomerically pure diol was the only reaction product obtained (Table 1, entries 4, 6, 10, 13 and 17, and footnote d).

Concerning a possible mechanistic pathway for the reaction shown in the Scheme 1, we think that after the first lithiation, the chloro-lithio intermediate **2** with X = Cl initially formed, which has a great tendency to undergo elimination of lithium chloride (see above, especially for $n = 2, 3$), can also react with the electrophile present in the reaction medium to give the chloro-alkoxide **5**. This new intermediate suffers then a new chlorine-lithium exchange to afford the functionalised organolithium species **6**, which in the presence of the electrophile gives the corresponding dialkoxide **7**, precursor of the diols **4** by final hydrolysis (Chart 2). On the other hand, the participation of dilithium intermediates of the type **1** could be ruled out because the second lithiation of the already chlorinated organolithium intermediate is much more difficult than either the decomposition by elimination or the reaction with the electrophile present in the reaction medium.¹³ The reaction conditions [(a) low temperature, (b) slow addition of the reagents (see section 4.2 in the Experimental part), and (c) Barbier-type conditions] are essential for the preparation of diols **4** from the corresponding 1,n-dihaloalkane **3**.

Table 1. Double lithiation of 1,n-dichloroalkanes **3a**. Preparation of compounds **4** (Method A)

Entry	n	Electrophile	Product ^a		Yield (%) ^b
			No.	Structure	
1	2	PhCHO	4a		23 ^c
2	2	Et ₂ CO	4b		18
3	2	(CH ₂) ₇ CO	4c		9
4	2	(-)-menthone	4d		25 ^d
5	3	PhCHO	4e		20 ^c
6	3	(-)-menthone	4f		15 ^d
7	4	Bu ^t CHO	4g		79 ^c
8	4	Et ₂ CO	4h		45
9	4	(CH ₂) ₄ CO	4i		62
10	4	(-)-menthone	4j		67 ^d
11	5	Et ₂ CO	4k		46
12	5	(CH ₂) ₄ CO	4l		57
13	5	(-)-menthone	4m		63 ^d
14	6	Bu ^t CHO	4n		64 ^c
15	6	PhCHO	4o		78 ^c
16	6	(CH ₂) ₅ CO	4p		65
17	6	(-)-menthone	4q		72 ^d

^a All products **4** were >95% pure (GLC and/or 300 MHz ¹H NMR) and were fully characterised by spectroscopic means (IR, ¹H and ¹³C NMR, and LR and HR mass spectrometry).

^b Isolated yields of compounds **4** after column chromatography (silica gel, hexane/ethyl acetate).

^c Obtained as a *ca.* 1:1 mixture of diastereomers (NMR).

^d The diastereomer shown in this table was exclusively obtained (see Text).

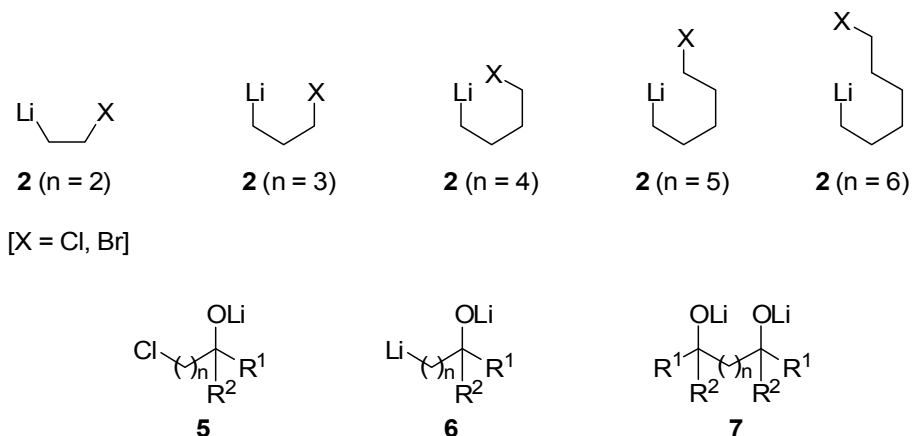


Chart 2.

The double lithiation under the same reaction conditions (Method A) of other starting materials, such as 1-bromo-*n*-chloroalkanes **3b** and 1,*n*-dibromoalkanes **3c** (both commercially available) was also studied. The results of this comparative study are summarised on Table 2. In general, yields are lower for compounds **3b** and **3c**, dichloroderivatives **3a** being the best substrates in this kind of processes. In the case of 1-bromo-*n*-chloroalkanes **3b**, we think that after the first lithiation, the chloro-lithio intermediate **2** with X = Cl is formed due to the higher reactivity of the carbon-bromine bond toward the lithiation reagent. We have reported recently on the selective monolithiation of bromo chloro alkanes (**2**, $n = 4, 5$ and 6) (carbon-bromine bond undergoes reductive cleavage faster than carbon-chlorine bond) and also on the one-pot tandem introduction of two different electrophiles under careful reaction conditions.⁷

2.2. Lithiation of 1,*n*-dihaloalkanes **3** under Grignard-type reaction conditions (Method B)

In order to determine the stability of the intermediates **2** (X = Cl, Br; Chart 2), we studied the lithiation of compounds **3a-c** in the absence of the electrophile (Grignard-type conditions). So, there would be a correlation between the yield of compounds **4** and the stability of the corresponding intermediates **2**. The reaction of compounds **3a-c** with an excess of lithium (1:10 molar ratio; theoretic 1:4 molar ratio) and a catalytic amount of DTBB (1:0.1 molar ratio, 2.5 mol %) in THF at -78°C for 1 h, followed by addition of 2.2 equivalents of a carbonyl compound at the same temperature and final hydrolysis with water at temperatures ranging between -78°C and room temperature (Method B), would lead to the expected diols **4** (Scheme 1 and Table 2).

In the case of 1,2-dihaloderivatives **3a-c** ($n = 2$, entries 1-3, Table 2), intermediates **2** ($n = 2$) decomposed rapidly before to a second lithiation took place, so after addition of 3-pentanone as electrophile, nothing of the expected diol **4b** was isolated nor detected by tandem GC/MS analysis. That indicates, as previously commented, that intermediates of type **2** ($n = 2, 3$) show a high tendency to undergo elimination. Such elimination takes place almost exclusively (Scheme 1, Table 2, entries 1-3) even in the presence of the electrophile (Barbier-type conditions), this probably being the main reason for the low yields. The possible participation of β -haloradicals in the synthesis of 1,4-diols **4** can not be completely ruled out.

Intermediates **2** with $n = 3$ seem to be also highly unstable because 1,5-diol **4e** was not observed after addition of benzaldehyde as electrophile (Table 2, entries 4-6).

Very low yield was also obtained from 1,4- and 1,5-dihaloalkanes **3a-c** ($n = 4, 5$) when 3-pentanone was used as electrophile, the expected reaction products **4h** and **4k** being not isolated but detected by tandem GC/MS (Table 2, entries 7-9 and 10-12). That indicates that 4-halo- and 5-haloalkyllithium intermediates (**2**, n

= 4, 5, X = Cl, Br) were not stable species under this reaction conditions. Finally, when benzaldehyde was used as electrophile, low yields of diol **4o** were obtained from 1,6-dichloro- and 1-bromo-6-chlorohexanes **3a** and **3b** ($n = 6$) (Table 2, entries 13 and 14), meanwhile, diol **4o** was not detected when starting from 1,6-dibromohexane (**3c**, $n = 6$) (Table 2, entry 15). Paying attention to these experimental results, we can assume that the 6-chloro derivative (**2**, $n = 6$, X = Cl) is more stable than the 6-bromoalkyllithium intermediate **2** ($n = 6$, X = Br) under the commented reaction conditions. The best yields of 1,4-, 1,6-, 1,7- and 1,8-diols **4** were obtained from dichloroalkanes **3a** ($n = 2, 4, 5$ and 6). The preparation of 1-chloro-4-lithiobutane¹⁴ (**2**, $n = 4$, X = Cl) and 1-chloro-6-lithiobutane¹⁵ (**2**, $n = n$, X = Cl) by monolithiation of the corresponding n -chloro-1-iodoalkanes with butyllithium have been previously reported.

Table 2. Double lithiation of 1, n -dihaloalkanes **3a-c**. Preparation of compounds **4**

Entry	Starting material [X-(CH ₂) _n -Y]				Electrophile	Product ^a Yield (%) ^b		No.	Structure
	No.	X	Y	n		Method A	Method B		
1	3a	Cl	Cl	2	Et ₂ CO	18	0	4b	
2	3b	Cl	Br	2		12	0		
3	3c	Br	Br	2		2 ^c	0		
4	3a	Cl	Cl	3	PhCHO	20	0	4e	
5	3b	Cl	Br	3		7	0		
6	3c	Br	Br	3		23	0		
7	3a	Cl	Cl	4	Et ₂ CO	45	3 ^c	4h	
8	3b	Cl	Br	4		31	2 ^c		
9	3c	Br	Br	4		22	0		
10	3a	Cl	Cl	5	Et ₂ CO	46	4 ^c	4k	
11	3b	Cl	Br	5		30	0		
12	3c	Br	Br	5		16	0		
13	3a	Cl	Cl	6	PhCHO	78	23	4o	
14	3b	Cl	Br	6		67	17		
15	3c	Br	Br	6		53	0		

^a All products **4** were >95% pure (GLC and/or 300 MHz ¹H NMR) and were fully characterised by spectroscopic means (IR, ¹H and ¹³C NMR, and LR and HR mass spectrometry).

^b Isolated yields of compounds **4** after column chromatography (silica gel, hexane/ethyl acetate).

^c Yield determined by GLC analysis.

3. Conclusions

In conclusion, we report here for the first time the controlled lithiation of 1, n -dihaloalkanes under DTBB-promoted conditions, which allows the preparation of symmetrically substituted diols **4** by using carbonyl compounds as electrophiles. The reaction is especially of interest for $n = 2, 3$ (even working with low yields in all cases)¹⁶ due to the outstanding problems concerning the decomposition of the halogen-lithio intermediates by elimination, which are partially overcome in this study. The best yields are always obtained starting from 1, n -dichloro alkanes **3a**.

4. Experimental

4.1. General

All reactions were carried out under an atmosphere of argon in oven-dried glassware. All reagents were commercially available (Acros, Aldrich) and were used without further purification. Commercially available anhydrous THF (99.9%, water content $\leq 0.006\%$, Acros) was used as solvent in all the lithiation reactions. IR spectra were measured (film) with a Nicolet Impact 400 D-FT Spectrometer. NMR spectra were recorded with a Bruker AC-300 or a Bruker ADVANCE DRX-500 using CDCl_3 as the solvent. LRMS and HRMS were measured with Shimadzu GC/HS QP-5000 and Finigan MAT95 S spectrometers, respectively. The purity of volatile products and the chromatographic analyses (GLC) were determined with a flame ionisation detector and a 12 m capillary column (0.2 mm diam., 0.33 μm film thickness), using nitrogen (2 mL/min) as carrier gas, $T_{\text{injector}} = 275\text{ }^\circ\text{C}$, $T_{\text{detector}} = 300\text{ }^\circ\text{C}$, $T_{\text{column}} = 60\text{ }^\circ\text{C}$ (3 min) and 60-270 $^\circ\text{C}$ (15 $^\circ\text{C}/\text{min}$), $P = 40\text{ kPa}$. Specific rotations were determined with a PerkinElmer 341 digital polarimeter.

4.2. Double lithiation of compounds **3a-c** in the presence of a carbonyl compound as electrophile (Barbier-type reaction conditions, Method A). Preparation of diols **4**.

Isolation of compounds 4. Method A: General procedure. To a blue suspension of lithium powder (0.070 g, 10 mmol) and a catalytic amount of DTBB (0.027 g, 0.1 mmol) in THF (3 mL) was slowly added a solution of the corresponding 1,n-dihaloalkane **3a-c** (1.0 mmol) and the corresponding carbonyl compound ($\text{R}^1\text{R}^2\text{CO}$, 3.0 mmol) in THF (1.2 mL) during *ca.* 3 h at $-78\text{ }^\circ\text{C}$. After the addition, the reaction mixture was stirred for 15 min at the same temperature. Then, it was hydrolysed with water (4 mL) and extracted with ethyl acetate ($3 \times 10\text{ mL}$). The organic layer was dried over anhydrous magnesium sulfate and evaporated (15 Torr). The residue was purified by column chromatography (silica gel; hexane/ethyl acetate) to yield pure products **4**. Yields and structures are included in Tables 1 and 2. Physical and spectroscopic data as well as literature references follow.

4.2.1. 1,4-Diphenylbutane-1,4-diol (4a).¹⁷ Diastereomeric mixture: Colourless oil; R_f 0.19 (hexane/ethyl acetate: 2/1); ν (film) 3580-3170 (OH), 3060, 3029, 2935, 2875, 1460 cm^{-1} ; δ_{H} 1.43 (2H, quintet, $J = 7.9\text{ Hz}$, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.75-1.81 (4H, m, CH_2CH_2), 2.94 (2H, br s, $2 \times \text{OH}$), 4.63-4.67 (2H, m, $2 \times \text{CHOH}$), 7.23-7.31 (10H, m, ArH); δ_{C} 35.0, 35.9 (CH_2), 74.05, 74.45 (CHOH), 125.8, 127.35, 127.4, 128.35, 144.45 (ArC); m/z 224 ($\text{M}^+ - \text{H}_2\text{O}$, 13%), 120 (73), 118 (100), 107 (38), 105 (22), 104 (16), 79 (48), 77 (44).

4.2.2. 3,6-Diethyloctane-3,6-diol (4b).¹⁸ Colourless oil; R_f 0.21 (hexane/ethyl acetate: 2/1); ν (film) 3520-3190 (OH), 2972, 2935, 2880, 1460 cm^{-1} ; δ_{H} 0.86 (12H, t, $J = 7.5\text{ Hz}$, $4 \times \text{CH}_3$), 1.45 [4H, s, $(\text{CH}_2)_2$], 1.48 [8H, q, $J = 7.5\text{ Hz}$, $2 \times \text{CH}_3\text{CH}_2$], 1.75 (2H, br s, $2 \times \text{OH}$); δ_{C} 7.8 (CH_3), 30.9, 31.3 (CH_2), 74.4 (COH); m/z 166 ($\text{M}^+ - 2\text{H}_2\text{O}$, 1%), 156 (11), 155 (100), 137 (52), 98 (33), 95 (18), 87 (56), 83 (26), 69 (31), 57 (91), 55 (30); HRMS: $\text{M}^+ - \text{H}_2\text{O}$, found 184.1833. $\text{C}_{12}\text{H}_{24}\text{O}$ requires 184.1827.

4.2.3. 1-[2-(1-Hydroxycyclooctyl)ethyl]cyclooctanol (4c).¹⁹ White solid; mp 118-119 $^\circ\text{C}$ (dichloromethane/hexane); R_f 0.16 (hexane/ethyl acetate: 2/1); ν (KBr) 3470-3230 (OH), 2932, 2919, 2852, 1460 cm^{-1} ; δ_{H} 1.25-1.78 (34H, m, $16 \times \text{CH}_2$, $2 \times \text{OH}$); δ_{C} 22.4, 25.0, 28.25, 34.2, 36.3 (CH_2), 74.65 (COH); m/z 264 ($\text{M}^+ - \text{H}_2\text{O}$, 5%), 193 (42), 180 (29), 127 (100), 122 (46), 110 (54), 109 (56), 95 (29), 81 (63), 67 (51), 55 (59).

4.2.4. (1S,2S,5R,1'S,2'S,5'R)-1-[2-(1'-Hydroxy-2'-isopropyl-5'-methylcyclohexyl)ethyl]-2-isopropyl-5-methylcyclohexanol (4d). White solid; mp 122-123 $^\circ\text{C}$ (dichloromethane/hexane) (found: C, 77.96; H, 12.37. $\text{C}_{22}\text{H}_{42}\text{O}_2$ requires: C, 78.05; H, 12.50); R_f 0.64 (hexane/ethyl acetate: 2/1); ν (KBr) 3510-3280 (OH), 2954, 2965, 2868, 1455, 1371 cm^{-1} ; δ_{H} 0.85-1.00 (20H, m, $6 \times \text{CH}_3$, $2 \times \text{CH}$), 1.05-1.67 (13H, m), 1.70-1.81 (6H, m), 1.90-2.15 (3H, m); δ_{C} 18.1 (CH_3), 19.9 (CH_3), 20.4 (CH_2), 22.5, 23.5 (CH_3), 24.3 (CH_2), 24.7, 25.25, 25.3 (CH), 25.8 (CH_2), 28.0, 29.85 (CH), 33.9, 35.05, 46.8, 47.1 (CH_2), 47.4, 54.4 (CH), 75.2, 75.4 (COH); m/z 320

($M^+ - H_2O$, 8%), 236 (17), 235 (100), 217 (18), 166 (21), 155 (64), 150 (51), 138 (51), 136 (31), 123 (30), 109 (21), 108 (17), 95 (51), 81 (42), 69 (38), 55 (29). $[\alpha]_D^{20} = -15.9^\circ$ (c 0.80, dichloromethane).

4.2.5. 1,5-Diphenylpentane-1,5-diol (4e).²⁰ Diastereomeric mixture: Colourless oil; R_f 0.19 (hexane/ethyl acetate: 2/1); ν (film) 3530-3180 (OH), 3062, 3029, 2980, 2938, 2865, 1454 cm^{-1} ; δ_H 1.43 (2H, quintet, $J = 7.9$ Hz, $CH_2CH_2CH_2$), 1.52-1.81 (4H, m, $2 \times CH_2CH$), 2.56 (2H, br s, $2 \times OH$), 4.58 (2H, t, $J = 7.3$ Hz, $2 \times CHOH$), 7.23-7.33 (10H, m, ArH); δ_C 22.05, 22.15, 38.6, 38.7 (CH_2), 74.1, 74.3 ($CHOH$), 125.8, 127.4, 128.35, 144.7 (ArC); m/z 238 ($M^+ - H_2O$, 4%), 129 (22), 105 (20), 104 (100), 91 (18), 77 (21).

4.2.6. (1S,2S,5R,1'S,2'S,5'R)-1-[3-(1'-Hydroxy-2'-isopropyl-5'-methylcyclohexyl)propyl]-2-isopropyl-5-methylcyclohexanol (4f). Colourless oil; R_f 0.71 (hexane/ethyl acetate: 2/1); ν (film) 3630-3340 (OH), 2952, 2868, 1464, 1373 cm^{-1} ; δ_H 0.82-1.78 (42H, m), 2.06-2.11 (2H, m); δ_C 18.0 (CH_2), 18.15 (CH_3), 20.5 (CH_2), 22.4, 23.6 (CH_3), 25.5, 28.0 (CH), 35.1, 41.9, 46.7 (CH_2), 48.1 (CH), 75.0 (COH); m/z 334 ($M^+ - H_2O$, 1%), 165 (15), 164 (100), 163 (18), 149 (26), 137 (25), 135 (35), 121 (27), 109 (38), 107 (17), 95 (53), 93 (26), 83 (17), 81 (58), 69 (48), 67 (34), 55 (56), 43 (56), 41 (58); HRMS: $M^+ - H_2O$, found 334.3233. $C_{23}H_{42}O$ requires 334.3236. $[\alpha]_D^{20} = +4.2^\circ$ (c 1.07, dichloromethane).

4.2.7. 2,2,9,9-Tetramethyldecane-3,8-diol (4g).^{10c} Diastereomeric mixture: White solid; mp 113-114 °C (dichloromethane/hexane) (found: C, 72.70; H, 13.39. $C_{14}H_{30}O_2$ requires: C, 72.99; H, 13.39); R_f 0.44 (hexane/ethyl acetate: 2/1); ν (KBr) 3580-3220 (OH), 2972, 2865, 1470, 1390, 1371 cm^{-1} ; δ_H 0.89 (18H, s, $6 \times CH_3$), 1.26-1.54 (10H, m, $4 \times CH_2$, $2 \times OH$), 3.20 (2H, dd, $J = 8.3, 2.1$ Hz, $2 \times CHOH$); δ_C 25.6 (CH_3), 26.9, 27.1, 31.4 (CH_2), 34.9 (C), 79.7, 79.9 ($CHOH$); m/z 212 ($M^+ - H_2O$, 1%), 155 (24), 137 (100), 99 (17), 97 (25), 95 (49), 83 (24), 81 (69), 71 (31), 69 (46), 67 (17), 57 (77), 55 (19).

4.2.8. 3,8-Diethyldecane-3,8-diol (4h).²¹ White solid; mp 72-73 °C (dichloromethane/hexane); R_f 0.25 (hexane/ethyl acetate: 2/1); ν (KBr) 3520-3230 (OH), 2963, 2943, 2878, 1461 cm^{-1} ; δ_H 0.85 (12H, t, $J = 7.5$ Hz, $4 \times CH_3$), 1.27-1.40 [10H, m, $(CH_2)_4$, $2 \times OH$], 1.46 (8H, q, $J = 7.5$ Hz, $4 \times CH_2$); δ_C 7.75 (CH_3), 24.0, 31.0, 38.15 (CH_2), 74.6 (COH); m/z 194 ($M^+ - 2H_2O$, 1%), 183 (13), 165 (65), 109 (23), 97 (43), 95 (20), 87 (100), 85 (24), 69 (38), 57 (77), 55 (21).

4.2.9. 1-[4-(1-Hydroxycyclopentyl)butyl]cyclopentanol (4i).²² White solid; mp 98-99 °C (dichloromethane/hexane) (found: C, 74.20; H, 11.75. $C_{14}H_{26}O_2$ requires: C, 74.29; H, 11.58); R_f 0.13 (hexane/ethyl acetate: 2/1); ν (KBr) 3440-3180 (OH), 2957, 2869, 1434 cm^{-1} ; δ_H 1.43-1.81 (26H, m, $12 \times CH_2$, $2 \times OH$); δ_C 23.7, 25.2, 39.55, 41.4 (CH_2), 82.4 (COH); m/z 208 ($M^+ - H_2O$, 1%), 121 (14), 113 (13), 108 (100), 95 (15), 93 (31), 85 (28), 79 (12), 67 (31), 55 (18).

4.2.10. (1S,2S,5R,1'S,2'S,5'R)-1-[4-(1'-Hydroxy-2'-isopropyl-5'-methylcyclohexyl)butyl]-2-isopropyl-5-methylcyclohexanol (4j). White solid; mp 56-57 °C (dichloromethane/hexane) (found: C, 78.21; H, 12.54. $C_{24}H_{46}O_2$ requires: C, 78.63; H, 12.65); R_f 0.69 (hexane/ethyl acetate: 2/1); ν (KBr) 3610-3330 (OH), 2941, 2866, 1455, 1366 cm^{-1} ; δ_H 0.83-0.98 (20H, m, $6 \times CH_3$, $2 \times CH$), 1.06-1.52 (17H, m), 1.60-1.77 (6H, m), 1.86-2.17 (3H, m); δ_C 18.1 (CH_3), 20.5 (CH_2), 22.4, 23.6 (CH_3), 24.7 (CH_2), 25.45, 28.0 (CH), 35.1, 41.3, 46.8 (CH_2), 47.7 (CH), 75.05 (COH); m/z 348 ($M^+ - H_2O$, 25%), 330 (12), 196 (18), 194 (19), 178 (78), 163 (27), 155 (78), 137 (100), 135 (49), 95 (46), 83 (15), 81 (54), 69 (49), 55 (30). $[\alpha]_D^{20} = +6.1^\circ$ (c 0.84, dichloromethane).

4.2.11. 3,9-Diethylundecane-3,9-diol (4k). White solid; mp 82-83 °C (dichloromethane/hexane); R_f 0.27 (hexane/ethyl acetate: 2/1); ν (KBr) 3450-3210 (OH), 2968, 2933, 2878, 1466 cm^{-1} ; δ_H 0.85 (12H, t, $J = 7.5$ Hz, $4 \times CH_3$), 1.25-1.42 [12H, m, $(CH_2)_5$, $2 \times OH$], 1.45 (8H, q, $J = 7.5$ Hz, $4 \times CH_2$); δ_C 7.7 (CH_3), 23.3, 30.9, 30.95, 38.1 (CH_2), 74.55 (COH); m/z 208 ($M^+ - 2H_2O$, 2%), 197 (17), 179 (64), 123 (21), 111 (42), 109 (28), 97 (20), 95 (28), 87 (100), 85 (31), 69 (45), 57 (90), 55 (26).

4.2.12. 1-[5-(1-Hydroxycyclopentyl)pentyl]cyclopentanol (4l).²³ Colourless oil; R_f 0.18 (hexane/ethyl acetate: 2/1); ν (film) 3530-3210 (OH), 2968, 2933, 2859, 1462 cm^{-1} ; δ_H 1.26-1.82 (28H, m, $13\times\text{CH}_2$, $2\times\text{OH}$); δ_C 23.8, 24.6, 30.7, 39.65, 41.4 (CH_2), 82.6 (COH); m/z 222 ($\text{M}^+-\text{H}_2\text{O}$, 1%), 204 (6), 136 (20), 135 (62), 123 (20), 122 (100), 121 (26), 108 (34), 95 (45), 93 (47), 85 (77), 81 (49), 80 (58), 67 (71), 57 (29), 55 (51).

4.2.13. (1S,2S,5R,1'S,2'S,5'R)-1-[5-(1'-Hydroxy-2'-isopropyl-5'-methylcyclohexyl)pentyl]-2-isopropyl-5-methylcyclohexanol (4m). White solid; mp 68-69 °C (dichloromethane/hexane) (found: C, 78.23; H, 12.60. $\text{C}_{25}\text{H}_{48}\text{O}_2$ requires: C, 78.88; H, 12.71); R_f 0.74 (hexane/ethyl acetate: 2/1); ν (KBr) 3560-3390 (OH), 2949, 2866, 2840, 1469, 1368 cm^{-1} ; δ_H 0.86-0.91 (18H, m, $6\times\text{CH}_3$), 1.03-1.11 (4H, m), 1.22-1.49 (18H, m), 1.62-1.77 (6H, m), 2.03-2.12 (2H, m); δ_C 18.1 (CH_3), 20.45 (CH_2), 22.45, 23.6 (CH_3), 23.9 (CH_2), 25.45, 28.0 (CH), 31.0, 35.1, 41.3, 46.8 (CH_2), 47.6 (CH), 75.1 (COH); m/z 362 ($\text{M}^+-\text{H}_2\text{O}$, 14%), 344 (13), 319 (26), 208 (19), 165 (45), 155 (64), 137 (100), 123 (14), 109 (30), 97 (18), 95 (47), 81 (51), 69 (42), 55 (25). $[\alpha]_D^{20} = +5.8^\circ$ (c 0.91, dichloromethane).

4.2.14. 2,2,11,11-Tetramethyldodecane-3,10-diol (4n).⁷ Diastereomeric mixture: White solid; mp 104-105°C (dichloromethane/hexane) (found: C, 74.99; H, 13.81. $\text{C}_{16}\text{H}_{34}\text{O}_2$ requires: C, 74.36; H, 13.26); R_f 0.58 (hexane/ethyl acetate: 2/1); ν (KBr) 3580-3210 (OH), 2970, 2864, 1469, 1389, 1367 cm^{-1} ; δ_H 0.89 (18H, s, $6\times\text{CH}_3$), 1.25-1.55 (14H, m, $6\times\text{CH}_2$, $2\times\text{OH}$), 3.18 (2H, dd, $J = 9.9, 2.0$ Hz, $2\times\text{CHOH}$); δ_C 25.7 (CH_3), 27.1, 29.7, 31.4, 31.45 (CH_2), 34.9 (C), 79.9, 79.95 (CHOH); m/z 240 ($\text{M}^+-\text{H}_2\text{O}$, 1%), 183 (22), 165 (29), 109 (100), 97 (23), 95 (62), 83 (58), 81 (22), 71 (29), 69 (39), 67 (17), 57 (74), 55 (24).

4.2.15. 1,8-Diphenyloctane-1,8-diol (4o).⁷ Diastereomeric mixture: White solid; mp 83-84°C (dichloromethane/hexane); R_f 0.30 (hexane/ethyl acetate: 2/1); ν (KBr) 3520-3180 (OH), 3083, 3058, 3022 cm^{-1} (ArH); δ_H 1.19-1.69 (14H, m, $6\times\text{CH}_2$, $2\times\text{OH}$), 4.54 (2H, dd, $J = 7.2, 6.1$, $2\times\text{CHOH}$), 7.21-7.29 (10H, m, $2\times\text{ArH}$); δ_C 25.1, 28.8, 38.4 (CH_2), 73.9 (CHOH), 125.3, 126.8, 127.8, 144.3 (ArC); m/z 280 ($\text{M}^+-\text{H}_2\text{O}$, 2 %), 207 (37), 174 (64), 158 (15), 117 (52), 107 (100), 105 (26), 104 (83), 91 (30), 79 (61), 77 (36).

4.2.16. 1-[6-(1-Hydroxycyclohexyl)hexyl]cyclohexanol (4p).²³ White solid; mp 89-90°C (dichloromethane/hexane) (found: C, 76.11; H, 12.36. $\text{C}_{18}\text{H}_{34}\text{O}_2$ requires: C, 76.54; H, 12.13); R_f 0.35 (hexane/ethyl acetate: 2/1); ν (KBr) 3570-3240 (OH), 2945, 1442 cm^{-1} ; δ_H 1.25-1.60 (34H, m, $16\times\text{CH}_2$, $2\times\text{OH}$); δ_C 22.2, 22.7, 25.8, 30.2, 37.3, 42.3 (CH_2), 71.3 (COH); m/z 246 ($\text{M}^+-2\text{H}_2\text{O}$, 13%), 166 (26), 109 (21), 99 (100), 96 (39), 95 (20), 94 (21), 83 (17), 82 (17), 81 (59), 67 (24), 55 (35).

4.2.17. (1S,2S,5R,1'S,2'S,5'R)-1-[6-(1'-Hydroxy-2'-isopropyl-5'-methylcyclohexyl)hexyl]-2-isopropyl-5-methylcyclohexanol (4q). White solid; mp 54-55 °C (dichloromethane/hexane); R_f 0.77 (hexane/ethyl acetate: 2/1); ν (KBr) 3590-3370 (OH), 2952, 2866, 1455, 1366 cm^{-1} ; δ_H 0.86-0.91 (18H, m, $6\times\text{CH}_3$), 1.02-1.12 (4H, m), 1.22-1.49 (20H, m), 1.64-1.77 (6H, m), 2.05-2.10 (2H, m); δ_C 18.1 (CH_3), 20.4 (CH_2), 22.45, 23.6 (CH_3), 23.8 (CH_2), 25.4, 27.95 (CH), 30.2, 35.1, 41.3, 46.8 (CH_2), 47.5 (CH), 75.1 (COH); m/z 376 ($\text{M}^+-\text{H}_2\text{O}$, 38%), 358 (18), 333 (65), 315 (18), 222 (13), 179 (36), 155 (81), 137 (100), 123 (20), 109 (30), 97 (21), 95 (49), 81 (55), 69 (43), 55 (25); HRMS: $\text{M}^+-\text{H}_2\text{O}$, found 376.3707. $\text{C}_{26}\text{H}_{48}\text{O}$ requires 376.3705. $[\alpha]_D^{20} = +6.3^\circ$ (c 1.09, dichloromethane).

4.3. Double lithiation of compounds 3a-c followed by reaction with carbonyl compounds as electrophiles (Grignard-type reaction conditions, Method B). Preparation of diols 4.

Isolation of compounds 4. Method B: General procedure. To a blue suspension of lithium powder (0.070 g, 10 mmol) and a catalytic amount of DTBB (0.027 g, 0.1 mmol) in THF (3 mL) was added the corresponding 1,n-difunctionalised alkane **3a-c** (1.0 mmol) at -78 °C. The reaction mixture was stirred for 1 h at the same temperature and after that, the corresponding carbonyl compound (2.2 mmol) was added dropwise and after 15 min it was hydrolysed with water (4 mL) and extracted with ethyl acetate (3×10 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated (15 Torr). The residue was purified by column

chromatography (silica gel; hexane/ethyl acetate) to yield pure products **4**. Yields and structures are included in Table 2. Physical and spectroscopic data as well as literature references are shown above.

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GRAPHICAL ABSTRACT

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(n = 2-6): A comparative study

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